Molecular Dynamics III

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All-Atom Simulation and Continuum Elastic Theory of Gramicidin a in Binary Component Lipid Bilayers

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The linear gramicidins are a group of peptides with alternating L and D chirality that fold into β-helices. The prototypical gramicidin is [Val[1]] gramicidin A (gA), which has been extensively studied using electrophysiology, spectroscopy, and molecular dynamics simulations. gA channels form by transmembrane dimerization and have been used to examine the interactions between membrane proteins and their host bilayer. This study focuses on gA channels in lipid bilayers composed of two phosphatidylcholines with different acyl chain lengths. The bilayers were formed from equimolar mixtures of $DC_{16:1}PC+DC_{24:1}PC$ or $DC_{18:1}PC+DC_{22:1}PC$ mixture, as well as pure $DC_{20:1}PC$, all of which have the same average tail length. These gA-bilayer systems were simulated for 3.5 μs to explore the characteristics and energetics of lateral lipid redistribution around a protein. The simulations indicate: *i*) the overall bilayer thickness profile adjacent to the channel is similar in the three systems tested; *ii*) in the $DC_{16:1}PC+DC_{24:1}PC$ mixture, the shorter $DC_{16:1}PC$ is enriched by nearly a factor of two in the first lipid shell around the channel; *iii*) thickness matching is dominant, even when the disparity between lengths is large; and *iv*) the acyl chains adopt non-native conformations in order to match achieve hydrophobic matching between the gA dimer and the bilayer core. In contrast to the results in the $DC_{16:1}PC+DC_{24:1}PC$ mixture, enrichment in the $DC_{18:1}PC+DC_{22:1}PC$ mixture is statistically insignificant. The preference for the better matching lipid ($DC_{16:1}PC$) near the channel in the $DC_{16:1}PC+DC_{24:1}PC$ mixture can be explained by a continuum model that accounts for the energetic penalty associated with compressing the longer lipid ($DC_{24:1}PC$) to match the channel's hydrophobic length.

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Molecular Modeling of Paclitaxel Interacting with Membranes

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Cell membranes define a confined space for the cell and form an essential barrier from the surrounding environments. They also provide active/passive transport systems for some essential nutrients and small molecules. But it is unclear how most of hydrophobic drugs such as paclitaxel penetrate through the cell membranes. Paclitaxel has been shown to aggregate both in hydrophilic and hydrophobic environments. Additionally it has been suggested to contribute to pore formation in the membrane. Here we investigated interactions between paclitaxel and a model cell membrane of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) using molecular dynamics simulations. The change of free energy across the bilayer interface calculated by adaptive biasing force method showed good agreement with experimental data. We performed 300ns long simulations of POPC membranes with randomly inserted drugs up to 0.1 mole fraction. We compared the results with a separate set of simulations where the drugs were initially inserted at lattice points with a single orientation. Interestingly, the main baccatinic core and the three more hydrophobic phenyl rings showed different preferential positioning in the membrane along the z-axis. This was consistent with the rotation and orientation of the drug. The clustering of the drug molecules in the membrane, order parameters of lipid tails, and water penetration along with the drug clusters were analyzed. Modeling the transport of hydrophobic drugs into the cell through computational investigations will provide insights of the drug delivery process at a molecular level.

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Mechanism of Cx26-G45E Deafness Mutant Dysregulation Explored by Molecular Dynamics Simulations

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To explore the mechanism by which Ca^{2+} blocks ionic conductance during tissue injury, we recently solved the X-ray crystal structures of the Cx26 gap junction channel with and without bound Ca^{2+}. The two structures were nearly identical, ruling out a large-scale steric mechanism for channel block. Also, the pore diameter was ~15 Å, sufficient for the passage of hydrated ions. The sites for Ca^{2+} coordination reside at the interface between adjacent subunits, near the entrance to the extracellular gap. Ca^{2+} binding occurs by local conformational shifts of Ca^{2+}-chelating residues. Molecular dynamics simulations and electrostatic calculations suggest that Ca^{2+} induces an electrostatic barrier to the passage of cations. We used MD simulations to explore the mechanism of channelopathy in the G45E mutant. The simulations suggest that the additional acidic side-chain at each of the channel-lining Ca^{2+} binding sites is unable to contribute to Ca^{2+} coordination. We propose that the additional negative charge contributed by the glutamate carboxylate disrupts normal Ca^{2+}-dependent electrostatic regulation of Cx26 ion selectivity and permeability.

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Drug Extrusion Process of Mate Multidrug Efflux Transporter Revealed by Molecular Dynamics Simulations

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MATE (the Multidrug And Toxic compound Extrusion) is one of the five multidrug efflux transporter super-families. It is featured as primary secondary active transporter and comprises of 12 trans-membrane helices. The first and last six transmembrane helices (TMs) form N-lobe and C-lobe domains, showing a two-fold rotational symmetry. It is considered that the drug release/capture related motions are characterized by switching of inward/outward-facing conformations (rocker-switch model).

Recently, multiple structures of the MATE from P.furiosus (PfMATE), has been determined by X-ray crystallography in outward-facing conformation. Two distinct structures 'Straight' and 'Bent' are characterized by conformations of TM1. Furthermore, PfMATE is shown to be H^+ driven antiporter, suggesting that D41 and D184 in N-lobe are involved as important proton pathway. It is also interesting that MATE has the hydrophobic surface of inner cavity, since other multidrug transporters exhibit hydrophilic. The sharply opened interface to the lipid molecules suggests the possibilities that the lipid molecules intensively interact with the inside of the cavity.

To further elucidate the drug release mechanism in outward facing stage, we adopted several promising simulation methods, continuum electrostatic analysis to predict protonation states, a number of independent all-atom Molecular Dynamics (MD) simulations by changing conditions (initial conformations, protonations, lipid positions, etc.) for dynamics and interactions, and quantum mechanics calculation for drug forcefield development. Our results suggest that D41 is protonated in Straight, while D41 and D184 are both protonated in Bent. Furthermore, we successfully observed multiple drug release events in some conditions of MD simulations. In the poster presentation, we will report and discuss the dynamics and interactions of PfMATE revealed by different conditions of MDs. We will also discuss the insights of the drug release mechanism of PfMATE obtained by the simulations.

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Exploring the Elastic Properties of Bilayer Membranes using Molecular Dynamics Simulations

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Local membrane deformation has been implicated in regulating a variety of cellular processes, such as ion channel function and vesicle fusion. In this work, we show how molecular dynamic simulations can be used alone or in conjunction with the continuum elastic model to estimate membrane elastic properties. Detail analysis allowed us to divide the energetic cost associated with the partial or complete extraction of a DOPE lipid from a POPC bilayer into two main contributions: a) the elastic deformation of the membrane, involving displacement of neighboring lipids, and b) the solvation energy associated to the exposure of the acyl chains to the water phase. Membrane elastic deformation was observed in molecular detail, and structural information from the simulations was used with the continuum elastic model to estimate an effective membrane spring constant independently from the energy parameters of the simulations. The membrane spring constant was also calculated from the potential of mean force and a good agreement was